CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 075079

Trade Name : OXYBUTYNIN CHLORIDE TABLETS USP 5MG

Generic Name: Oxybutynin Chloride Tablets USP 5mg

Sponsor : Vintage Pharmaceuticals, Inc.

Approval Date: October 31, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 075079

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	Included	Pending Completion	Not Prepared	Not Required
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Medical Review(s)				
Chemistry Review(s)	X			
EA/FONSI				
Pharmacology Review(s)				
Statistical Review(s)				
Microbiology Review(s)				
Clinical Pharmacology Biopharmaceutics Review(s)				
Bioequivalence Review(s)	X			
Administrative Document(s)				
Correspondence				

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 075079

APPROVAL LETTER

ANDA 75-079

OCT 31 1997

Vintage Pharmaceuticals, Inc.
Attention: Rebecca A. Thurman
3241 Woodpark Blvd.
Charlotte, NC 28206

Dear Madam:

This is in reference to your abbreviated new drug application dated February 18, 1997 submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Oxybutynin Chloride Tablets USP, 5 mg.

Reference is also made to your amendments dated August 18 and 26, 1997.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Oxybutynin Chloride Tablets USP, 5 mg to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Ditropan Tablets, 5 mg of Hoechst Marion Roussel, Inc.). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

/S/ 10/31/97

Douglas L. Spørn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 075079

FINAL PRINTED LABELING

Vintage®

100 TABLETS
10 X 10 UNIT DOSE

OXYBUTYNIN CHLORIDE TABLETS, USP
5 mg

CAUTION: Federal law prohibits dispensing without prescription.

NDC 0254-4835-27

NDC 0254-4835-27

OXYBUTYNIN CHLORIDE TABLETS, USP
5 mg

EACH TABLET CONTAINS:
Oxybutynin Chloride, USP ..... 5 mg
USUAL DOSAGE: See package insert.
DISPENSE in a tight, light-resistant container as defined in the USP/NF.
STORE at controlled room temperature 15°-30° C (59°-86° F).
WARNING: This unit-dose package is not child-resistant.
Keep out of reach of children.

Mfg. by
VINTAGE PHARMACEUTICALS, INC.
CHARLOTTE, NC 28206
Rev. 6/98
R1

CAUTION: Federal law prohibits dispensing without prescription.

100 TABLETS
10 X 10 UNIT DOSE

NDC 0254-4835-27

OXYBUTYNIN CHLORIDE TABLETS, USP
5 mg

CAUTION: Federal law prohibits dispensing without prescription.

100 TABLETS
10 X 10 UNIT DOSE

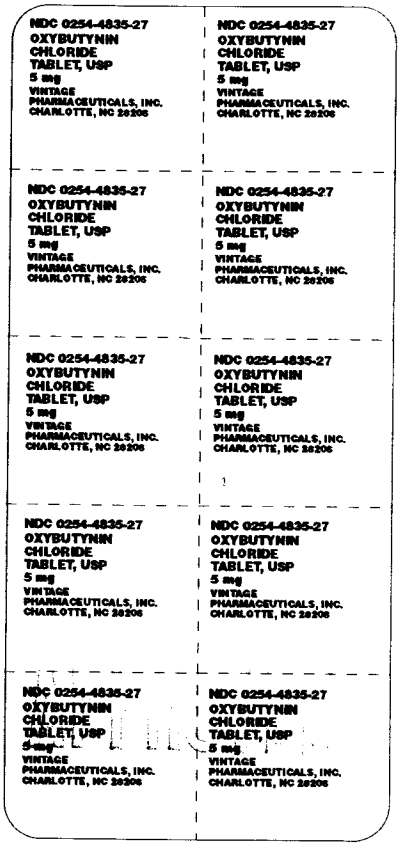
NDC 0254-4835-27

OXYBUTYNIN CHLORIDE TABLETS, USP
5 mg

CAUTION: Federal law prohibits dispensing without prescription.

100 TABLETS
10 X 10 UNIT DOSE

Vintage® Vintage® Vintage®



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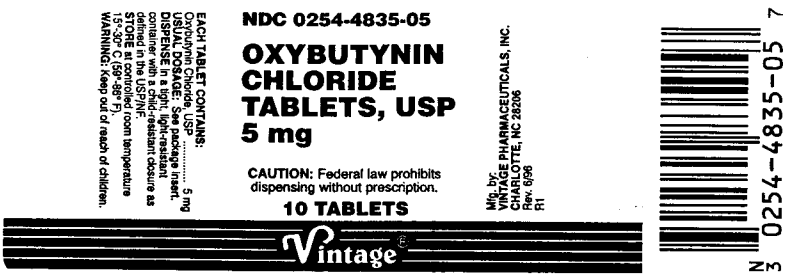
NDC 0254-4835-05
OXYBUTYNIN CHLORIDE TABLETS, USP 5 mg
CAUTION: Federal law prohibits dispensing without prescription.
10 TABLETS
Vintage®
EACH TABLET CONTAINS: Oxybutynin Chloride, USP ..... 5 mg
USUAL DOSAGE: See package insert.
DISPENSE in a tight, light-resistant container as defined in the USP/NF.
STORE at controlled room temperature 15°-30° C (59°-86° F).
WARNING: Keep out of reach of children.
Mfg. by: VINTAGE PHARMACEUTICALS, INC. CHARLOTTE, NC 28206 Rev. 6/96 R1
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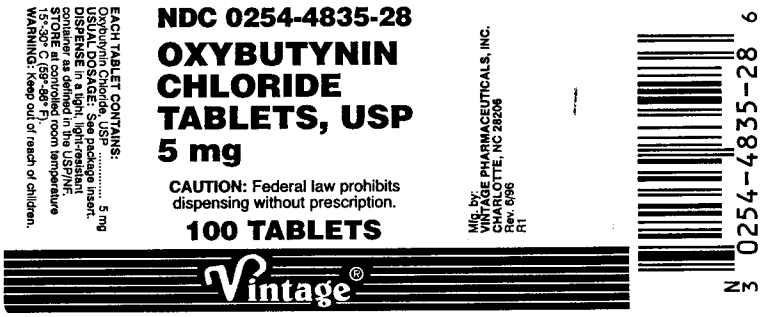
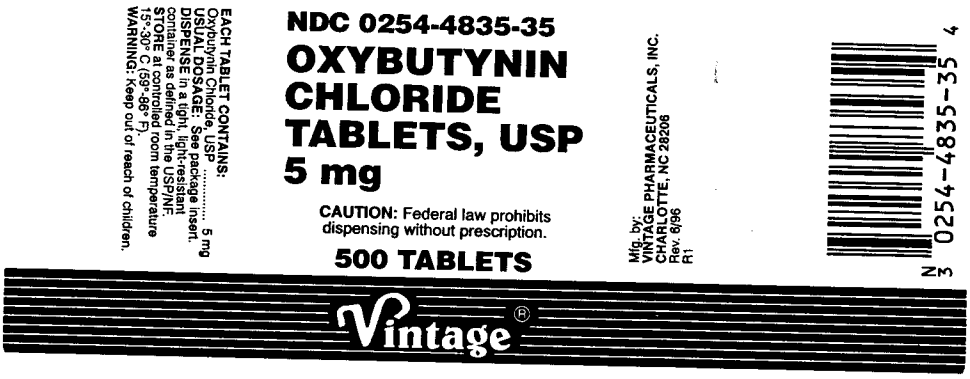
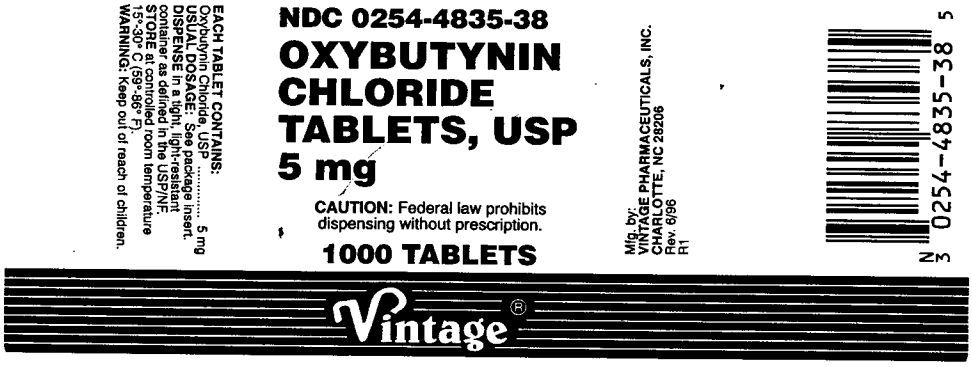

NDC 0254-4835-28
OXYBUTYNIN CHLORIDE TABLETS, USP 5 mg
CAUTION: Federal law prohibits dispensing without prescription.
100 TABLETS
Vintage®
EACH TABLET CONTAINS: Oxybutynin Chloride, USP ..... 5 mg
USUAL DOSAGE: See package insert.
DISPENSE in a tight, light-resistant container as defined in the USP/NF.
STORE at controlled room temperature 15°-30° C (59°-86° F).
WARNING: Keep out of reach of children.
Mfg. by: VINTAGE PHARMACEUTICALS, INC. CHARLOTTE, NC 28206 Rev. 6/96 R1
N 3 0254-4835-28 6

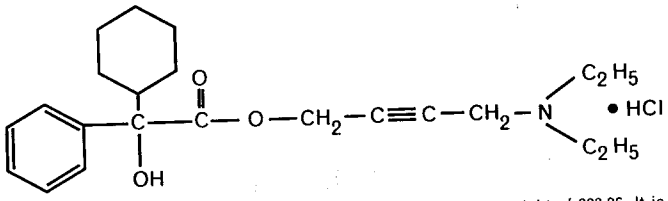

NDC 0254-4835-35
OXYBUTYNIN CHLORIDE TABLETS, USP 5 mg
CAUTION: Federal law prohibits dispensing without prescription.
500 TABLETS
Vintage®
EACH TABLET CONTAINS: Oxybutynin Chloride, USP ..... 5 mg
USUAL DOSAGE: See package insert.
DISPENSE in a tight, light-resistant container as defined in the USP/NF.
STORE at controlled room temperature 15°-30° C (59°-86° F).
WARNING: Keep out of reach of children.
Mfg. by: VINTAGE PHARMACEUTICALS, INC. CHARLOTTE, NC 28206 Rev. 6/96 R1
N 3 0254-4835-35 4


NDC 0254-4835-38
OXYBUTYNIN CHLORIDE TABLETS, USP 5 mg
CAUTION: Federal law prohibits dispensing without prescription.
1000 TABLETS
Vintage®
EACH TABLET CONTAINS: Oxybutynin Chloride, USP ..... 5 mg
USUAL DOSAGE: See package insert.
DISPENSE in a tight, light-resistant container as defined in the USP/NF.
STORE at controlled room temperature 15°-30° C (59°-86° F).
WARNING: Keep out of reach of children.
Mfg. by: VINTAGE PHARMACEUTICALS, INC. CHARLOTTE, NC 28206 Rev. 6/96 R1
N 3 0254-4835-38 5

OXYBUTYNIN CHLORIDE USP TABLETS

DESCRIPTION

Chemically, oxybutynin chloride is 4-(Diethylamino)-2-butynyl (±)-α-phenylcyclohexaneglycolate hydrochloride. The molecular formula of oxybutynin chloride is $C_{22}H_{31}NO_3 \cdot HCl$. The molecular formula appears below:



Oxybutynin chloride is a white crystalline solid with a molecular weight of 393.96. It is readily soluble in water and acids, but relatively insoluble in alkalis.

Each tablet, for oral administration contains 5 mg of oxybutynin chloride. In addition, each tablet contains the following inactive ingredients FD&C Blue #1 lake, magnesium stearate, microcrystalline cellulose, and pregelatanized starch.

Therapeutic Category: Antispasmodic, anticholinergic.

CLINICAL PHARMACOLOGY

Oxybutynin chloride exerts direct antispasmodic effect on smooth muscle and inhibits the muscarinic action of acetylcholine on smooth muscle.

Oxybutynin chloride exhibits only one fifth of the anticholinergic activity of atropine on the rabbit detrusor muscle, but four to ten times the antispasmodic activity. No blocking effects occur at skeletal neuromuscular junctions or autonomic ganglia (antinicotinic effects).

Oxybutynin chloride relax bladder smooth muscle. In patients with conditions characterized by involuntary bladder contractions, cystometric studies have demonstrated that oxybutynin chloride increases bladder (vesical) capacity, diminishes the frequency of uninhibited contractions of the detrusor muscle, and delays the initial desire to void. Oxybutynin chloride thus decreases urgency and the frequency of both incontinent episodes and voluntary urination.

Oxybutynin chloride was well tolerated in patients administered the drug in controlled studies of 30 days' duration and in uncontrolled studies in which some of the patients received the drug for 2 years. Pharmacokinetic information is not currently available.

INDICATIONS AND USAGE

Oxybutynin chloride tablets are indicated for the relief of symptoms of bladder instability associated with voiding in patients with uninhibited neurogenic or reflex neurogenic bladder (i.e., urgency, frequency, urinary leakage, urge incontinence, dysuria).

CONTRAINDICATIONS

Oxybutynin chloride tablets are contraindicated in patients with untreated angle closure glaucoma and in patients with untreated narrow anterior chamber angles since anticholinergic drugs may aggravate these conditions.

It is also contraindicated in partial or complete obstruction of the gastrointestinal tract, paralytic ileus, intestinal atony of the elderly or debilitated patient, megacolon, toxic megacolon complicating ulcerative colitis, severe colitis, and myasthenia gravis. It is contraindicated in patients with obstructive uropathy and in patients with unstable cardiovascular status in acute hemorrhage.

Oxybutynin chloride tablets are contraindicated in patients who have demonstrated hypersensitivity to the product.

WARNINGS

Oxybutynin chloride, when administered in the presence of high environmental temperature, can cause heat prostration (fever and heat stroke due to decreased sweating).

Diarrhea may be an early symptom of incomplete intestinal obstruction, especially in patients with ileostomy or colostomy. In this instance treatment with oxybutynin chloride tablets would be inappropriate and possibly harmful.

Oxybutynin chloride may produce drowsiness or blurred vision. The patient should be cautioned regarding activities requiring mental alertness such as operating a motor vehicle or other machinery or performing hazardous work while taking this drug.

Alcohol or other sedative drugs may enhance the drowsiness caused by oxybutynin chloride.

PRECAUTIONS

Oxybutynin chloride should be used with caution in the elderly and in all patients with autonomic neuropathy, hepatic or renal disease. Oxybutynin chloride may aggravate the symptoms of hyperthyroidism, coronary heart disease, congestive heart failure, cardiac arrhythmias, hiatal hernia, tachycardia, hypertension, and prostatic hypertrophy. Administration of oxybutynin chloride to patients with ulcerative colitis may suppress intestinal motility to the point of producing a paralytic ileus and precipitate or aggravate toxic megacolon, a serious complication of the disease.

Carcinogenesis, Mutagenesis, Impairment of Fertility.

A 24-month study in rats at dosages up to approximately 400 times the recommended human dosage showed no evidence of carcinogenicity.

Oxybutynin chloride showed no increase of mutagenic activity when tested in *Schizosaccharomyces pompholiciformis, Saccharomyces cerevisiae and Salmonella typhimurium* test systems. Reproduction studies in the hamster, rabbit, rat, and mouse have shown no definite evidence of impaired fertility.

Pregnancy Category B. Reproduction studies in the hamster, rabbit, rat, and mouse have shown no definite evidence of impaired fertility or harm to the animal fetus. The safety of oxybutynin chloride administered to women who are or who may become pregnant has not been established. Therefore, oxybutynin chloride should not be given to pregnant women unless, in the judgement of the physician, the probable clinical benefits outweigh the possible hazards.

Nursing Mothers. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when oxybutynin chloride is administered to a nursing woman.

Pediatric Use. The safety and efficacy of oxybutynin chloride administration has been demonstrated for pediatric patients 5 years of age and older (see DOSAGE AND ADMINISTRATION). However, as there is insufficient clinical data for pediatric populations under age 5, oxybutynin chloride is not recommended for this age group.

ADVERSE REACTIONS

Following administration of oxybutynin chloride, the symptoms that can be associated with the use of other anticholinergic drugs may occur:

Cardiovascular: Palpitations, tachycardia, vasodilatation

Dermatologic: Decreased sweating, rash

Gastrointestinal/Genitourinary: Constipation, decreased gastrointestinal motility, dry mouth, nausea, urinary hesitance and retention

Nervous System: Asthenia, dizziness, drowsiness, hallucinations, insomnia, restlessness

Ophthalmic: Amblyopia, cycloplegia, decreased lacrimation, mydriasis

Other: Impotence, suppression of lactation

OVERDOSAGE

The symptoms of overdosage with oxybutynin chloride may be any of those seen with other anticholinergic agents. Symptoms may include signs of central nervous system excitation (e.g., restlessness, tremor, irritability, convulsions, delirium, hallucinations), flushing, fever, nausea, vomiting, tachycardia, hypotension or hypertension, respiratory failure, paralysis, and coma.

In the event of an overdose or exaggerated response, treatment should be symptomatic and supportive. Maintain respiration and induce emasis or perform gastric lavage (emasis is contraindicated in precomatose, convulsive, or psychotic state). Activated charcoal may be administered as well as a cathartic. Physostigmine may be considered to reverse symptoms of anticholinergic intoxication. Hyperpyrexia may be treated symptomatically with ice bags or other cold applications and alcohol sponges.

DOSAGE AND ADMINISTRATION

Adults: The usual dose is one 5-mg tablet two to three times a day. The maximum recommended dose is one 5-mg tablet four times a day.

Pediatric patients over 5 years of age: The usual dose is one 5-mg tablet two times a day. The maximum recommended dose is one 5-mg tablet three times a day.

HOW SUPPLIED

Oxybutynin chloride tablets, 5 mg, are round, light blue, scored tablets debossed with "4853 and V" on one side separated by a horizontal score and plain on the other side.

The tablets are supplied in:

bottles of 10	NDC #0254-4835-05
bottles of 100	NDC #0254-4835-28
bottles of 500	NDC #0254-4835-35
bottles of 1000	NDC #0254-4835-38
unit dose identification paks of 100 tablets	NDC #0254-4835-27

Pharmacist: Dispense in tight, light-resistant container as defined in the USP.

Store at controlled room temperature 15—30°C (59—86°F).

Caution: Federal law prohibits dispensing without a prescription.

Manufactured by:
VINTAGE PHARMACEUTICALS, INC.
Charlotte, NC 28206

IN-135
Rev 8/97
R3

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 075079

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO. 2

2. ANDA #75-079

3. NAME AND ADDRESS OF APPLICANT

Vintage Pharmaceuticals Inc.
3241 Woodpark Blvd.
Charlotte, NC 28206

4. BASIS OF SUBMISSION

Accepted by OGD

5. SUPPLEMENT(s)

N/A

6. PROPRIETARY NAME

N/A

7. NONPROPRIETARY NAME

Oxybutynin Chloride

8. SUPPLEMENT(s) PROVIDE(s) FOR:

N/A

9. AMENDMENTS AND OTHER DATES:

2/18/97 - original submission
8/18/97 - amendment responding to OGD's Facsimile dated 7/18/97

10. PHARMACOLOGICAL CATEGORY

Antispasmodic, Anticholinergic

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

See review #1.

13. DOSAGE FORM

Tablet

14. POTENCY

5 mg

15. CHEMICAL NAME AND STRUCTURE

See USP XXIII, page 1127.

16. RECORDS AND REPORTS

N/A

17. COMMENTS

N/A

18. CONCLUSIONS AND RECOMMENDATIONS

Application is not approvable.

A. Chemistry issues are closed.

B. LABELING

Satisfactory 9/3/97. SNB

Review of the August 18, 1997 amendment - pending [redacted] /S/ [redacted]

C. BIOEQUIVALENCY STATUS

Satisfactory 10/3/97 SNB

Not Satisfactory. A letter dated August 18, 1997 was issued by the Division of Bioequivalence.

19. REVIEWER: [redacted] /S/

Shirley S. Brown

DATE COMPLETED:

8/29/97

August 22, 1997

[redacted] /S/

Labeling in 8/18/97 amendment found satisfactory per review of [redacted] on 9/4/97.

Bioequivalence found satisfactory based on review of amendment dated 8/26/97 and letter issued 10/9/97. 10/23/97.

[redacted] /S/

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 075079

BIOEQUIVALENCE REVIEW(S)

ANDA 75-079

OCT - 9 1997

Vintage Pharmaceuticals
Attention: Rebecca Thurman
3241 Woodpark Blvd.
Charlotte, NC 28206

Dear Madam:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Oxybutynin Chloride Tablets USP, 5 mg.

1. The Division of Bioequivalence has completed its review and has no further questions at this time.

2. The dissolution testing will need to be incorporated into your stability and quality control programs as specified in USP 23.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

/S/

Rabindra N. Patnaik, Ph.D.
Acting Director,
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

OCT - 3 1997

Oxybutynin Chloride, USP
5 mg Tablets
ANDA #75-079
Reviewer: James Chaney
WP # 75079a.897

Vintage Pharmaceuticals, Inc.
Charlotte, NC
Submission Date:
February 18, 1997
August 26, 1997

Review Of An Amendment To The *in vivo* Bioequivalence Study Submitted February 18, 1997

Deficiency

In the *in vivo* bioequivalence study submitted February 18, 1997 the long term stability of the drug and metabolite in frozen plasma was not demonstrated. The firm was advised that stability data should be submitted on the drug product stored in frozen plasma at the temperature and over the period of time employed in the storage of the frozen samples in the bioequivalence study (at least five months).

Firm's Response

The stability in frozen plasma was established as shown in the following table.

Long-term Stability of Oxybutynin (Parent) and Desethyloxybutynin (Metabolite) in Frozen Plasma.			
Time	Date	Parent	Metabolite
		Theoretical Concentration Level (ng/ml)	
0	9/5/96	(b)4 - Confidential Business	
3 weeks	9/26/96		
9 weeks	11/12/96		
6 months	3/5/97		

Comment:

Dosing in this study began on 4/25/96 and the analytical study was completed on 9/27/96. The firm's establishment of stability of the drug product in frozen plasma under the conditions actually used in the bioequivalence study over the period of time exceeding the length of time the bioequivalence study samples were actually stored has been found acceptable by the Division of Bioequivalence.

Recommendations:

1. The single-dose, fasting bioequivalence study conducted by Vintage Pharmaceuticals, Inc. on its oxybutynin chloride, USP 5 mg Tablet, lot #003065 comparing it to Marion Merrell Dow's Ditropan Tablets 5 mg tablet, lot #K33750 has been found acceptable by the Division of Bioequivalence. The study results demonstrate that Vintage Pharmaceuticals' oxybutynin chloride, USP 5 mg Tablet is bioequivalent under fasting conditions to the reference product, Marion Merrell Dow's Ditropan Tablets 5 mg tablet.

2. The dissolution testing conducted by Vintage Pharmaceuticals, Inc. on its oxybutynin chloride, USP 5 mg tablet has been found acceptable. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of water at 37° C using USP 23 apparatus 2 (paddle) at 50 rpm. The test product should meet the following specifications:

   Not less than [redacted] (Q) of the labeled amount of oxybutynin in the dosage form is dissolved in 30 minutes.

[redacted] /S/

James E. Chaney, Ph.D.
Division of Bioequivalence
Review Branch I

RD INITIALED YCHua [redacted] /S/ 9/12/97
FT INITIALED YCHua

Concur: [redacted] /S/ Date: 10/3/97

Rabindra Patnaik, Ph.D.
Acting Director, Division of Bioequivalence

cc: ANDA 75-079 (original, duplicate), HFD-652 (Huang, Chaney), HFD-650 (Director), Drug File, Division File

JEC/090997/WP#75079a.897

AUG - 4 1997

Oxybutynin Chloride, USP
5 mg Tablets
ANDA #75-079
Reviewer: James Chaney
WP # 75079sd.297

Vintage Pharmaceuticals, Inc.
Charlotte, NC
Submission Date:
February 18, 1997

REVIEW OF AN IN VIVO FASTING BIOEQUIVALENCE STUDY AND IN VITRO DISSOLUTION TESTING DATA

I. INTRODUCTION:

Oxybutynin chloride is a synthetic tertiary amine which is chemically and pharmacologically similar to some anticholinergic, antispasmodic, local anesthetic, and antihistaminic compounds. It is used for relieving voiding symptoms in patients with uninhibited neurogenic and reflex neurogenic bladder.

Following an oral administration of a five mg oxybutynin chloride tablet, oxybutynin is rapidly absorbed with a Cmax of 8 ng/mL in less than one hour. The plasma concentrations show large intersubject variations with an elimination half-life of 2 hours.

A main metabolite, N-desethyloxybutynin, has similar pharmacological properties to the parent drug, has a peak level and Cmax greater than that of the parent drug.

Oxybutynin chloride is available in tablet (5 mg) and syrup (5 mg/5 mL) forms. The usual adult dosage is 5 mg two to three (not to exceed four) times daily.

II. OBJECTIVE

The purpose of this study was to compare the relative bioavailability of Vintage's oxybutynin chloride 5 mg tablets with those of Ditropan^{R} 5 mg tablets taken under fasting conditions in healthy, adult, male subjects.

III. INVESTIGATORS AND FACILITIES

Clinical Study
Director (b)4 - Confidential Business

Laboratories:
Study sar (b)4 - Confidential Business
direction
Samples for clinical safety analysis (urine drug screening, chemistry, hematology and urinalysis) were analyzed b (b)4 - Confidential Business
Statistical analysis was done by

IV. STUDY DATES

Dosing in this study began on 4/25/96 and the study was completed on 5/02/96.
The analytical study was completed between 9/16/96 and 9/27/96,

V. CLINICAL

Institutional Review Board: Th (b)4 - Confidential pproved this study prior to its commencement. A sample copy of the subject consent form was submitted. Information to ensure informed consent was presented to all subjects before the start of

the study.

Subject Selection: The 40 subjects who participated in this study were healthy males, in the age range of 18-50 years, and within 15% of their ideal weight as specified in the protocol. All subjects were selected based on the absence of any clinically significant findings in the medical history, physical examination, and clinical laboratory evaluations. All findings were determined to be not clinically significant for those subjects enrolled in the study.

Formulations:

Test (A) Two 5 mg oxybutynin chloride tablets (Vintage Pharmaceuticals, Lot #003065A, Exp. Date 5/97)

Reference (B) Two 5 mg Ditropan^{R} tablets (Marion Merrel Dow, Lot #K33750, Exp. date 4/99)

Restrictions: Prior to check-in for the study, the subjects were instructed not to take any prescribed medications for at least 14 days prior to the initial dosing and throughout the study. No OTC medications were permitted for 72 hours before dosing in each study period. No medications were permitted during confinement except those administered. Subjects were also instructed to abstain from any products containing alcohol or caffeine for 48 hours prior to dosing and throughout each confinement. None of the subjects reported taking any restricted substance within the time frames indicated.

During the confinement periods of the study, water was restricted from one hour before until one hour after dosing except for water (240 mL) administered with the dose. Water was permitted *ad lib* at all other times. Smoking was restricted from one hour before until two hours after each dose and for 30 minutes before each vital sign measurement.

Safety: Urine drug screens were performed at each check-in to test for alcohol, marijuana and cocaine metabolites.

Blood pressure (sitting), pulse rate, respiratory rate and oral temperature were measured before each dosing.

Blood pressure and pulse rate measurements (sitting) were obtained 3 hours after each dose (within ±30 minutes) and prior to release in each study period to monitor the health of the subjects. A brief physical examination was performed prior to the subject's release from the clinic in Period II.

Confinement, Meals: During the confinement periods of this study, the subjects were housed and fed at the clinical facility. Meals were provided on check-in day and completed at least 10 hours prior to scheduled dosing time.

During confinement (Day 1), standardized, caffeine-free meals or snacks were served at 4 and 10 hours after dosing. The same menu was used during each study period. A seven-day washout separated the dosings.

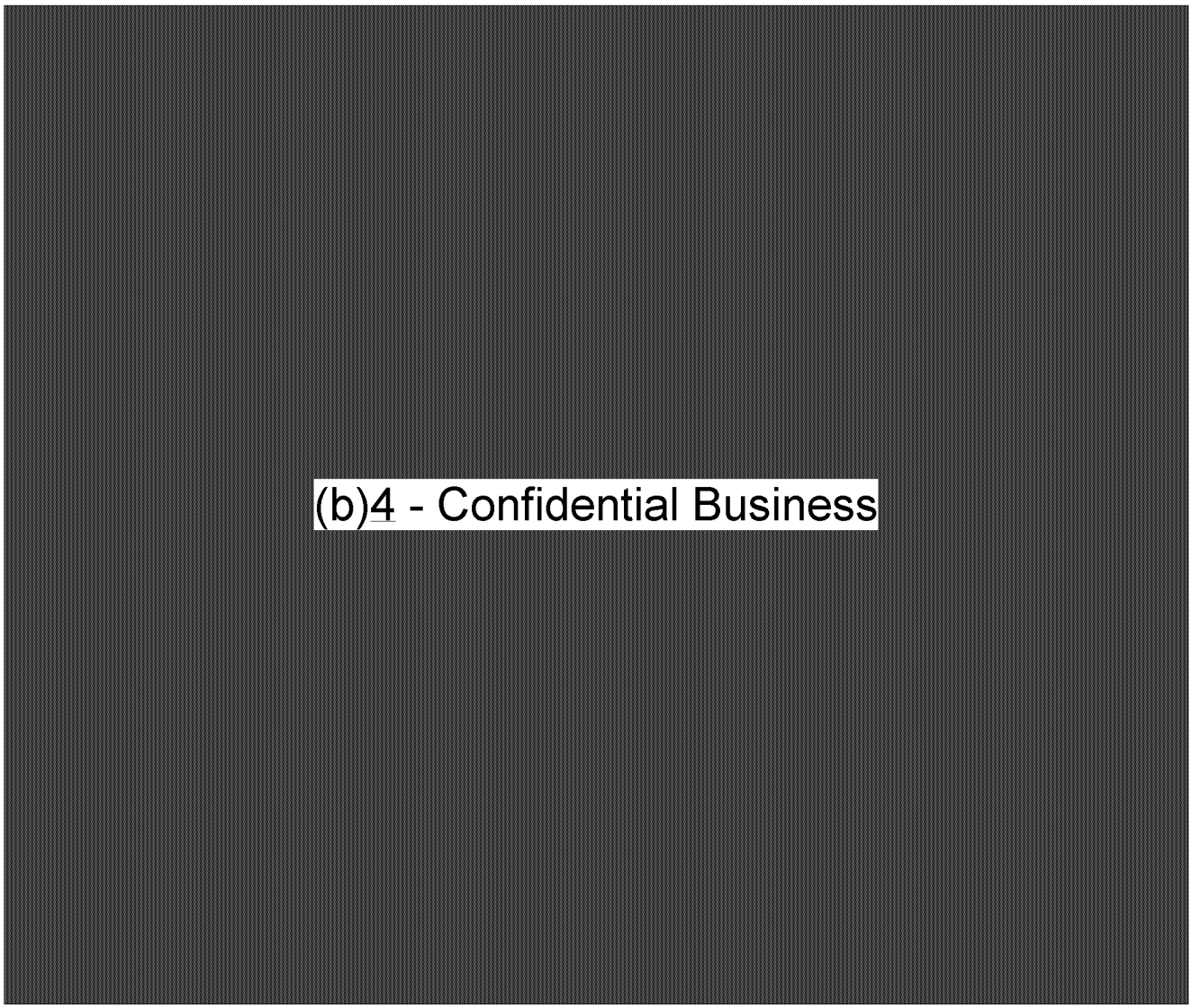
Blood sampling: In each period, blood samples were collected prior to dosing and at the following nominal times after dosing: 0.17, 0.33, 0.5, 0.67, 0.83, 1, 1.25, 1.5, 2, 3, 4, 5, 6, 8 and 10 hours. Pre-dose samples were collected within one hour before dosing. All plasma samples were stored frozen at -20°C (±5°) until transfer to the laboratory for analysis of oxybutynin and desethyloxybutynin.

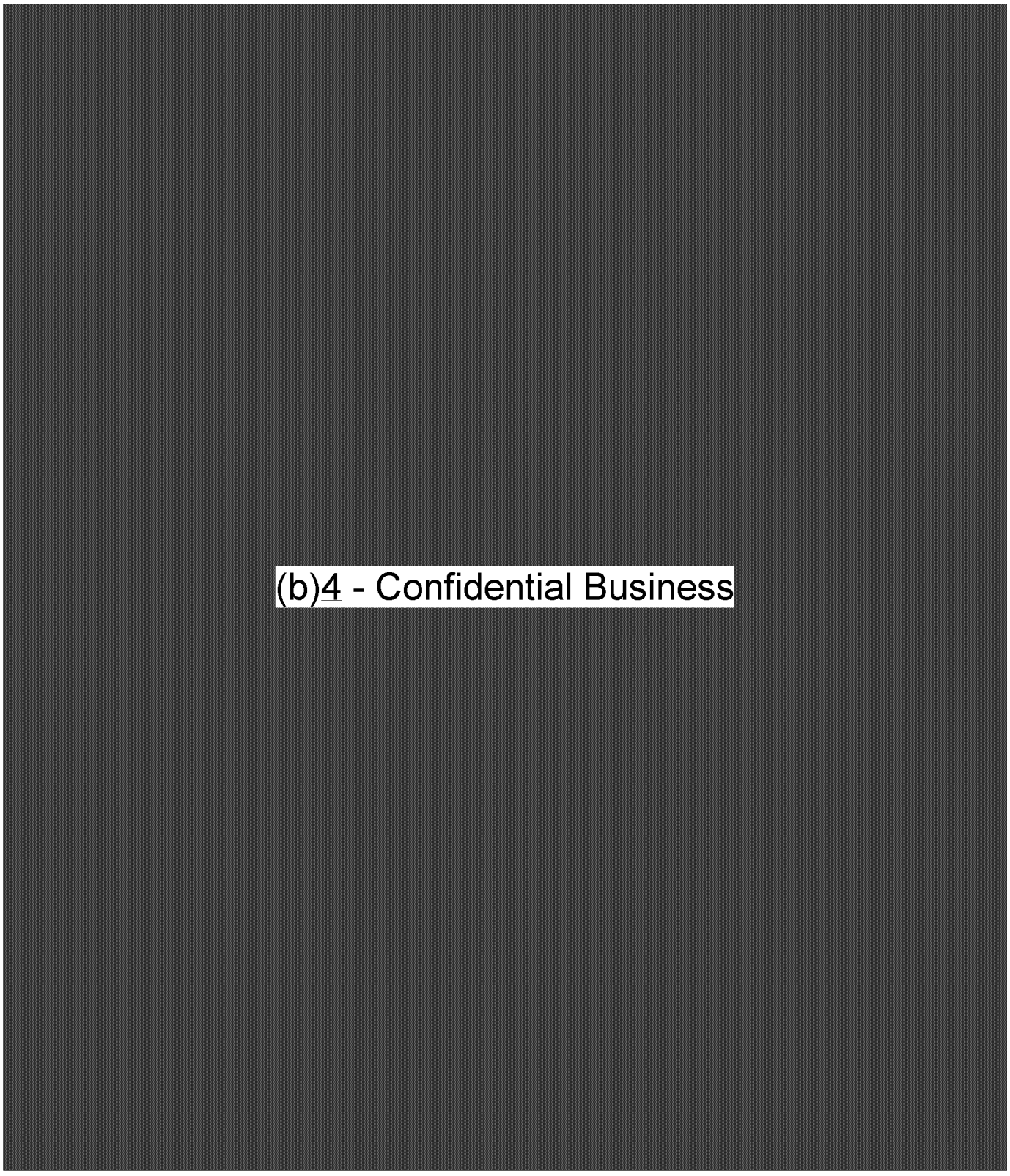
VI. PHARMACOKINETICS AND STATISTICAL ANALYSIS:

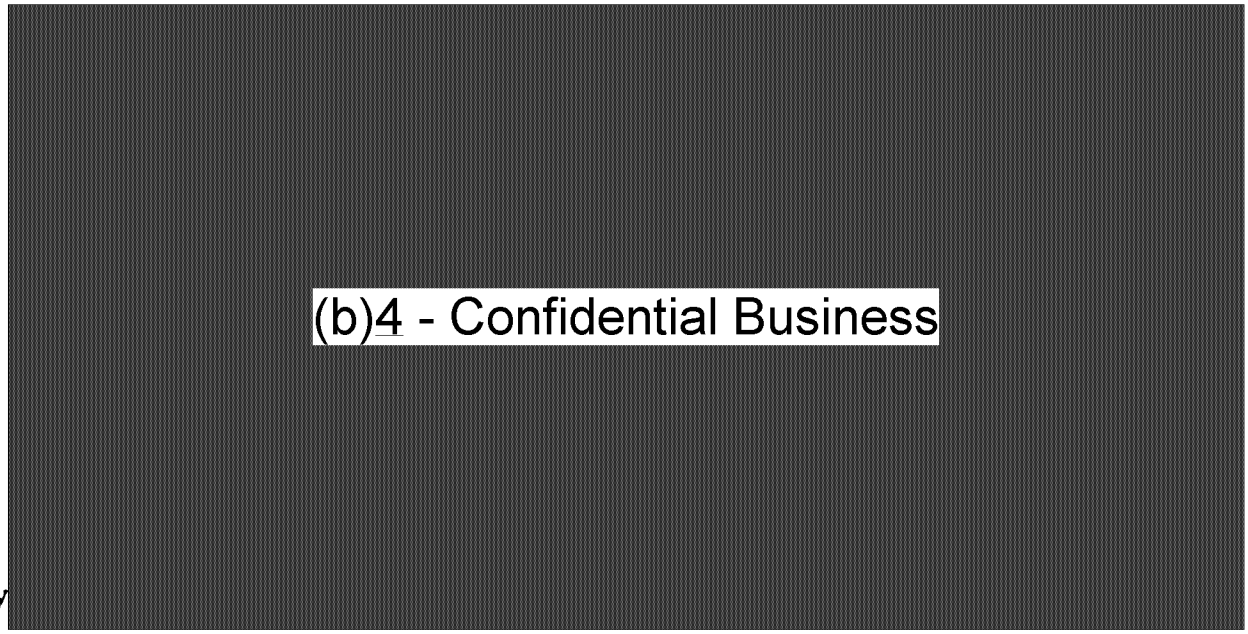
Statistical analyses were performed using the General Linear Models (GLM) procedure of the SAS statistical program. Hypothesis testing for treatment effects was conducted at $\alpha = 0.05$. The statistical model contained main effects of sequence, subject within sequence, period, and treatment. Sequence effects were tested against the type III mean square term for subjects within sequence. All other main effects were tested against the mean square error term.

Power for the pair-wise pharmacokinetic comparisons was calculated as the probability ($\alpha = 0.05$) of detecting a difference equal to 20% of the mean for the reference treatment in the comparison (or ratio of 1.25 for ln-transformed results). Confidence intervals (90%) for pair-wise area and peak concentration comparisons were calculated by the t-test approach (2,1-sided) at $\alpha = 0.10$ overall, $\alpha = 0.05$ each side.

VII. ANALYTICAL




(b)4 - Confidential Business



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VIII. STUDY RESULTS

A total of 40 subjects were entered into the study and 36 subjects completed the study. Subject 19 did not return for Period II. Subject 21 became dizzy during blood collections in Period I and was injured when he fell. Subjects 35 and 38 tested positive on their urine drug/alcohol screens at check-in to Period II.

The mean plasma concentrations for all time points for oxybutynin are shown in Table 5. A linear plot of the mean plasma concentration for oxybutynin as a function of time is shown in Figure 1. The pharmacokinetic data for oxybutynin are shown in Tables 6 and 7.

The mean plasma concentrations for all time points for desethyloxybutynin are shown in Table 8. A linear plot of the mean plasma concentration for desethyloxybutynin as a function of time is shown in Figure 2. The pharmacokinetic data for desethyloxybutynin are shown in Tables 9 and 10.

Mean test/reference ratios of the pharmacokinetic parameters AUC_{0-t}, AUC_{0-inf} and C_{max} for oxybutynin and desethyloxybutynin are within the range of 0.8 to 1.2. For the log transformed data, the 90% confidence intervals about the ratio of the test geometric mean to reference geometric mean are within 80% to 125% for both analytes.

Individual test/reference ratios of the pharmacokinetic parameters AUC_{0-t}, AUC_{0-inf} and C_{max} for oxybutynin are attached as Table 13. Individual AUC_{0-t}/AUC_{0-inf} ratios for oxybutynin are attached as Table 14. Individual test/reference ratios of the pharmacokinetic parameters AUC_{0-t}, AUC_{0-inf} and C_{max} for desethyloxybutynin are attached as Table 15. Individual AUC_{0-t}/AUC_{0-inf} ratios for desethyloxybutynin are attached as Table 16.

Table 5. Summary of oxybutynin statistical comparisons at each sampling time comparing Vintage's 5 mg oxybutynin chloride tablets (Test) vs. 5 mg Ditropan^{R} tablets (Reference) administered as 10 mg (2X5mg) doses under fasting conditions (n=36).

Time (Hour)	Least Squares Means (ng/ml)		
	Test	Reference	T/R
Pre-dose	0.00	0.00	-
0.17	2.65	0.97	2.73
0.33	8.38	7.09	1.18
0.50	11.12	12.62	0.88
0.67	10.71	12.36	0.87
0.83	9.75	11.04	0.88
1.00	8.32	9.41	0.88
1.25	6.64	7.72	0.86
1.50	5.48	6.37	0.86
2.00	4.18	4.58	0.91
3.00	2.63	2.78	0.95
4.00	1.51	1.74	0.87
5.00	0.84	1.01	0.83
6.00	0.41	0.56	0.73
8.00	0.11	0.18	0.61
10.00	0.03	0.06	0.50

Table 6. Comparisons of oxybutynin results for Vintage's 5 mg oxybutynin chloride tablets (Test) vs. 5 mg Ditropan^{R} tablets (Reference) administered as 10 mg (2X5mg) doses under fasting conditions (n=36).

Parameter	Least Squares Means [1]		Test/Ref Ratio	90% Confidence Interval	
	Test	Reference		Lower	Upper
AUC0-t (ng-hr/ml)	21.05	23.38	0.900	-	-
AUCinf (ng-hr/ml)	23.21	24.24	0.958	-	-
Cmax (ng/ml)	12.72	14.28	0.891	-	-
Tmax (hour)	0.62	0.69	0.896	-	-
Ke (1/hour)	0.4669	0.4702	0.993	-	-
Elimhalf (hour)	1.58	1.56	1.014	-	-
Ln-Transformed Data					
AUC 0-t (ng-hr/ml)	18.60	19.97	0.932	86.4	100.4
AUCinf (ng-hr/ml)	21.09	21.71	0.971	89.9	105.0
Cmax (ng/ml)	10.91	11.24	0.971	86.0	109.6

[1] Least squares geometric means for ln-transformed data.

Table 7. Comparisons of oxybutynin arithmetic mean results for Vintage's 5 mg oxybutynin chloride tablets (Test) vs. 5 mg Ditropan^R tablets (Reference) administered as 10 mg (2X5mg) doses under fasting conditions (n=36).

	TEST			REFERENCE			T/R
	Mean	N	CV	Mean	N	CV	
AUC0-t	20.865	36	50	23.254	36	58	0.90
AUC0-inf	22.827	29	47	24.958	25	47	0.91
Cmax	12.614	36	56	14.215	36	72	0.89
Tmax	0.620	36	36	0.692	36	34	0.90
Ke	0.478	29	22	0.468	25	22	1.02
T1/2	1.564	29	30	1.564	25	28	1.00
0 Hr	0.000	36	.	0.000	36	.	.
0.17 Hr	2.585	36	160	0.979	36	180	2.64
0.33 Hr	8.281	36	90	7.034	36	118	1.18
0.50 Hr	11.056	36	62	12.591	36	85	0.88
0.67 Hr	10.582	33	48	12.313	36	65	0.86
0.83 Hr	9.678	36	47	11.189	35	61	0.86
1.0 Hr	8.267	36	48	9.375	36	56	0.88
1.25 Hr	6.595	36	45	7.699	36	52	0.86
1.5 Hr	5.445	36	45	6.337	36	49	0.86
2 Hr	4.200	35	51	4.545	36	48	0.92
3 Hr	2.599	36	72	2.769	36	55	0.94
4 Hr	1.502	36	46	1.726	36	49	0.87
5 Hr	0.828	36	77	0.998	36	63	0.83
6 Hr	0.406	36	127	0.552	36	95	0.74
8 Hr	0.106	36	261	0.180	36	187	0.59
10 Hr	0.024	36	600	0.062	36	342	0.40
LAUC	2.916	36	18	2.388	36	20	1.22
LAUCinf	3.034	29	14	3.114	25	15	0.97
Lcmax	2.383	36	24	2.414	36	30	0.99

Table 8. Summary of desethyloxybutynin statistical comparisons at each sampling time comparing Vintage's 5 mg oxybutynin chloride tablets (Test) vs. 5 mg Ditropan^R tablets (Reference) administered as 10 mg doses under fasting conditions (n=36).

Time (Hours)	Least Squares Means (ng/ml)		
	Test	Reference	T/R
Pre-dose	0.00	0.00	-
0.17	7.36	1.80	4.09
0.33	53.18	31.84	1.67
0.50	92.24	82.66	1.12
0.67	102.54	102.57	1.00
0.83	103.53	102.65	1.01
1.00	96.34	98.09	0.98
1.25	84.37	88.71	0.95
1.50	76.27	80.12	0.95
2.00	64.86	66.53	0.97
3.00	51.48	50.63	1.02
4.00	36.84	38.82	0.95
5.00	26.60	28.60	0.93
6.00	19.75	20.28	0.97
8.00	10.09	10.57	0.95
10.00	4.10	4.80	0.85

Table 9. Comparisons of desethyloxybutynin results for Vintage's 5 mg oxybutynin chloride tablets (Test) vs. 5 mg Ditropan[R] tablets (Reference) administered as 10 mg doses under fasting conditions (n=36).

Parameter	Least Squares Means[1]		Test/Ref Ratio	90% Confidence Interval	
	Test	Reference		Lower	Upper
AUC 0-t (ng-hr/ml)	344.00	347.60	0.990	94.0	103.9
AUCinf (ng-hr/ml)	367.35	372.48	0.986	93.7	103.5
Cmax (ng/ml)	117.19	114.15	1.027	97.1	108.3
Tmax (hour)	0.80	0.92	0.877	-	-
Ke (1/hour)	0.3397	0.3386	1.003	-	-
Elimhalf (hour)	2.10	2.10	0.999	-	-
Ln-Transformed Data					
AUC 0-t (ng-hr/ml)	326.95	325.34	1.005	95.9	105.3
AUCinf (ng-hr/ml)	348.95	348.61	1.001	95.8	104.6
Cmax (ng/ml)	113.48	109.14	1.040	98.0	110.3

[1] Least squares geometric means for ln-transformed data

Table 10. Comparisons of desethyloxybutynin arithmetic mean results for Vintage's 5 mg oxybutynin chloride tablets (Test) vs. 5 mg Ditropan[R] tablets (Reference) administered as 10 mg doses under fasting conditions (n=36).

	TEST			REFERENCE			T/R
	N	Mean	CV	N	Mean	CV	
AUC0-t	36	342.69	35	36	346.28	39	0.99
AUC0-inf	36	365.87	35	36	371.11	40	0.99
Cmax	36	116.91	27	36	114.07	31	1.02
Tmax	36	0.80	53	36	0.91	52	0.88
Ke	36	0.34	19	36	0.34	17	1.01
T1/2	36	2.10	17	36	2.10	17	1.00
0 Hr	36	0.00	.	36	0.00	.	.
0.17 Hr	36	7.23	169	36	1.84	208	3.93
0.33 Hr	36	52.69	79	36	31.90	90	1.65
0.50 Hr	36	92.07	11	36	82.85	58	1.11
0.67 Hr	36	103.71	33	36	102.64	39	1.01
0.83 Hr	36	103.33	26	35	103.63	34	1.00
1.0 Hr	36	96.18	28	36	97.99	32	0.98
1.25 Hr	36	84.24	27	36	88.62	31	0.95
1.5 Hr	35	76.17	25	36	79.97	30	0.95
2 Hr	36	65.19	32	36	66.18	35	0.99
3 Hr	36	51.27	42	36	50.40	42	1.02
4 Hr	36	36.69	42	36	38.61	44	0.95
5 Hr	36	26.46	48	36	28.40	49	0.93
6 Hr	36	19.63	50	36	20.17	49	0.97
8 Hr	36	10.02	58	36	10.50	64	0.95
10 Hr	36	4.02	119	36	4.77	107	0.84
LAUC	36	5.79	5	36	5.78	6	1.00
LAUC0-inf	36	5.85	5	36	5.85	6	1.00
LCmax	36	4.73	5	36	4.69	6	1.01

[redacted](b)4 -[redacted]eported that no plasma was received from several Period I sampling times which were reported to have been collected in the clinic: 1.0 hr sample from Subject 08; and 0.667 hour samples from Subjects 26, 29 and 32. For these samples, labeled empty tubes were received at [redacted](b)4 -[redacted]devoid of matrix. Two samples were labeled as the 1.0 hour collection for Subject 14 in Period I. Based on graphical analysis of the pharmacokinetic profiles (drug and metabolite) of all subjects with missing samples, the values reported by [redacted](b)4 -[redacted]for the 1.0

hour sample from Subject 14, Period I, appeared to be the correct values for the 1.0 hour sample from Subject 08, Period I. The values reported as the duplicate 1.0 hour sample for Subject 14, Period I appeared to be the correct data for this subject. These sample value assignments were used in the pharmacokinetic and statistical analyses.

The subjects were monitored throughout the study for any adverse experiences. None of the adverse events experienced by the subjects during this study were judged as serious. A tabulation of all adverse events can be found in Table 17.

IX. FORMULATION

Vintage Pharmaceutical's formulation of its drug product, Oxybutynin Chloride, USP, 5 mg Tablets is summarized in Table 11.

(NOT FOR RELEASE UNDER FOI)

Table 11. Quantitative Composition: Lot #003065 (Bio-study Lot) Oxybutynin Chloride, USP, 5 mg Tablet

Ingredient	**Wt. per tablet**
Oxybutynin Chloride, USP (5% excess)	5.25 mg
Microcrystalline Cellulose, NF [redacted]	[redacted](b)4 - [redacted]
FD&C Blue #1 Lake	confidentia
Pregelatinized Starch, NF	
Magnesium Stearate, NF	
Total Tablet Weight	**165.00 mg**

X. DISSOLUTION TESTING (USP Method)

The dissolution testing results are shown in Table 12.

XI. COMMENTS

1. The possible mislabelling of one of the duplicate 1 hour samples from subject 14 of period I and the absence of samples from period I at 1 hour for subject 8 and at 0.667 hour for subjects 26, 29, and 32 leads to some question as to the validity of the data from these subjects, in view of the fact that the mean T_{max} values for the parent and metabolite fall in the range of 0.62 to 0.92 hour.

   Therefore data from subjects 8, 14, 26, 29 and 32 were deleted by the reviewer and the statistics were recalculated. The ratios of the test LSMEAN to the reference LSMEAN for AUC_{0-t}, AUC_{0-inf} and C_{max} remain within the acceptable range of 0.8-1.2 for oxybutynin and desethyloxybutynin. The 90% confidence intervals for log-transformed AUC_{0-t}, AUC_{0-inf} and C_{max} remain within the acceptable range of 80-125% for oxybutynin and desethyloxybutynin.

Recalculated mean T/Rs and confidence intervals after deleting 5 subjects.						
Analyte	T/R			Confidence Intervals		
	AUC0-t	AUCinf	Cmax	AUC0-t	AUCinf	Cmax
Parent	0.95	1.01	1.02	87.8-103.8	92.8-109.7	89.9-116.5
Metabolite	1.02	1.02	1.06	97.4-107.8	97.3-106.9	99.2-113.0

2. No long term stability data was submitted on the analytes stored in frozen plasma over the

period of time corresponding to the time and temperature at which the frozen plasma samples were actually stored in the bioequivalence studies.

3. A deviation to SOP G. 1004.05 "Entries in Notebooks, Forms and Logbooks" occurred when a write over was made in a logbook. This deviation is not expected to alter the results.

4. The pharmacokinetic parameters and statistics were calculated by the reviewer and were in satisfactory agreement with what the firm reported.

XII. DEFICIENCY

No long term stability data was submitted on the analytes stored in frozen plasma. Stability data should be submitted on the analytes (oxybutynin and desethyloxybutynin) stored in frozen plasma over the period of time corresponding to the time (at least five months) and temperature at which the frozen samples were actually stored in the bioequivalence studies.

RECOMMENDATIONS

1. The single-dose, fasting bioequivalence study conducted by Vintage Pharmaceuticals, Inc. on its oxybutynin chloride, USP 5 mg Tablet, lot #003065 comparing it to Marion Merrell Dow's Ditropan Tablets 5 mg tablet, lot #K33750 has been found incomplete by the Division of Bioequivalence due to the deficiency.

2. The dissolution testing conducted by Vintage Pharmaceuticals, Inc. on its oxybutynin chloride, USP 5 mg tablet has been found acceptable. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of water at 37° C using USP 23 apparatus 2 (paddle) at 50 rpm. The test product should meet the following specifications:

   Not less than (b)4(Q) of the labeled amount of oxybutynin in the dosage form is dissolved in 30 minutes.

The firm should be advised of the deficiency and the recommendations.

Table 12. In Vitro Dissolution Testing

Drug (Generic Name): Oxybutynin Chloride Tablets
Dose Strength: 5 mg
ANDA No.: 75-079
Firm: Vintage Pharmaceuticals, Inc.
Submission Date: February 18, 1997
File Name: 75079sd.297

I. Conditions for Dissolution Testing:

USP XXIII Basket: Paddle: X RPM: 50 No. Units Tested: 12
Medium: Deionized Water Volume: 900 mL
Specifications: NLT (b)4 (Q) of labeled amount in 30 minutes
Reference Drug: Ditropan Tablets 5 mg (Marion Merrell Dow)
Assay Methodology: (b)4 - Confidential

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot # 003065 Strength (mg) 5			Reference Product Lot # K33750 Strength(mg) 5		
	Mean	Range	%CV	Mean %	Range	%CV
8	71.7	(b)4 - Confident Business	2.3	68.5	(b)4 - Confidenti Business	5.3
15	84.7		2.1	80.3		3.4
23	87.6		2.6	85.4		3.6
30	90.1		2.6	87.5		3.2

FIG 1.

OXYBUTYNIN STUDY NO. 9627001B

LEAST-SQUARES MEAN OXYBUTININ PLASMA CONCENTRATIONS (N=36)

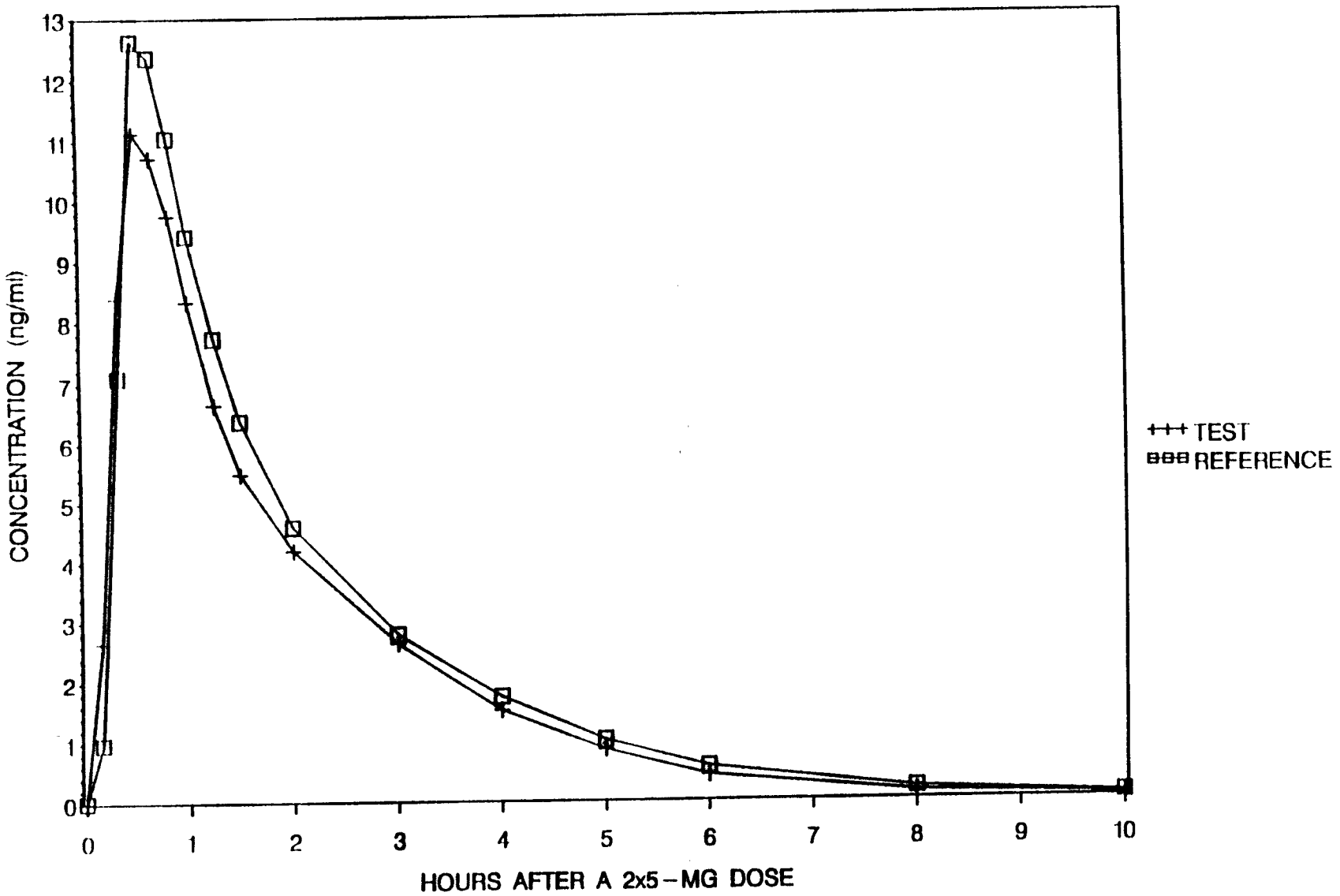

FIG 2.

OXYBUTYNIN STUDY NO. 9627001B

LEAST-SQUARES MEAN DESETHYLOXYBUTININ PLASMA CONCENTRATIONS (N=36)